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1. Your reference — IT/LT/N15089 — 21 JAN 2004

2. Patent application number *(The Patent Office will fill this part)* — 0401291.0

3. Full name , address and postcode of the or of each applicant *(underline all surnames)*

The School of Pharmacy
University of London
23-39 Brunswick Square
London WC1N 1AX, United Kingdom

Patents ADP number *(if you know it)* 61662430001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — **Method of Producing Microparticles**

5. Name of your agent *(if you have one)* — Williams Powell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Morley House, 26-30 Holborn Viaduct
London
EC1A 2BP

Patents ADP number *(if you know it)* 5830310001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country *(if you know it)*	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application.

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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system, placing much less mechanical stress on these labile molecules than the preparation of pellets or tablets would.

The Eudragits are commonly used pH-sensitive coatings for tablet, pellet and capsule systems and are soluble above different threshold pHs; L100-55 (pH 5.5), L100 (6.0), S100 (6.8) and P4135 (7.4). Previous attempts at formulating microparticles of L100 and S100 have been relatively unsuccessful, resulting in particles of poor morphology and control of drug release, and have involved complicated production methods involving homogenisation, careful control of temperature or rate of addition of surfactant.

Given the theoretical advantages of microparticulate systems over conventional dosage forms, the present applicant decided to try to overcome the problems that have led to the production of microparticles of poor morphology and control of drug release. It was decided to optimise the emulsification/solvent evaporation method for the production of Eudragit L/S100 microparticles, a commonly used method of microencapsulation.

The emulsification/solvent evaporation method is a conceptually simple, three step process. In step one, polymer is dissolved in a suitable solvent (into which the drug is dispersed, or preferentially dissolved), and emulsified into a non-solvent phase usually containing a surfactant to improve emulsion stability. In step two, solvent is allowed to evaporate, usually under agitation. Once this is complete, particles are solidified, and can be separated by filtration and cleaned up. The present applicant has discovered that the crucial step in the process for the formation of good particles is the formation of a stable emulsion in the early stages, and to achieve this the choice of surfactant can be considered key. It has also been found that the choice of solvent influences microparticle morphology depending on the rate at which it migrates from the polymer solution into the non-solvent phase and is removed by evaporation. The solubility of the polymer in the chosen solvent and boiling point are factors that affect how quickly the particles solidify. During this process the forming "particles" will evolve from being liquid emulsion

The chemicals used in the process are all widely available, relatively inexpensive and safe. We have shown microencapsulation to be possible using a mixture of organic solvents and, preferably, ethanol alone thus avoiding the use of more toxic solvents. The equipment used in the process is also widely available.

At present no method exists for the large-scale production of Eudragit L100 and S100 particles. Spray-drying has proved unsuccessful due to the thermoplastic nature of the polymers, and its tendency to form stringy aggregates. This leaves the method we have developed as the most feasible alternative.

A number of preferred embodiments of the present invention will now be disclosed, with reference to Figures 1 to 11, which show various scanning electron micrographs (SEMs) of examples and comparative examples of microparticles of drug/polymer mixtures.

Preliminary experiments were carried out to optimise the choice of solvent mixture using Span 85 as a surfactant. 30mL mixtures of acetone and either ethanol or methanol in different ratios were tried, and it was found that acetone/methanol mixtures worked better than acetone/ethanol, probably due to a faster evaporation of methanol resulting from a lower boiling point and reduced affinity for the polymer, Eudragit S100. When methanol alone was used, large, hollow, and sometimes, cracked particles were produced. Acetone alone did not produce any microparticles. Increasing the proportion of acetone reduced the size but seemed to increase the degree of aggregation. 20mL acetone/10mL methanol was the optimal solvent mixture as judged by SEM analysis, and it was decided to use this in future experiments, and change the surfactant.

Surfactants in, and close to, this range were therefore sourced, and a simple system using liquid paraffin as non-solvent was tried, with overhead propeller stirring from a Heidolph RZR1 stirrer calibrated to 1000rpm. A mixture of 30mL acetone/methanol (2:1) was

used to dissolve 3 grams Eudragit S100 polymer. Stirring and solvent evaporation were allowed to proceed overnight, and the product was collected by vacuum filtration through a sintered glass filter the next day, washed with three 50ml portions of hexane to remove traces of liquid paraffin, and dried in a vacuum oven for 24 hours. All experiments were carried out in triplicate, and the polymer used in the optimisation process was always Eudragit S100.

The following surfactants were initially employed at 1% concentration, and 2 and 3% if necessary; span 85 (HLB 1.8), span 80 (HLB 4.3), span 20 (HLB 8.6), Brij 92 (HLB 4.9), Brij 52(HLB 5.3), oleic acid (HLB 4.3) and sorbitan sesquioleate (Arlacel 83) (HLB 3.7).

Particles were firstly examined by optical microscopy (Nikon Microphot FXA) at x4 and x10 objective magnification, and images were captured using a JVC video camera. An indication of the overall morphology and degree of aggregation was possible, but to observe the surface characteristics of the microparticles in detail, SEMs of promising particles were taken. The microspheres were fixed on SEM adhesion pads, and coated with gold using a gold sputter module in a high-vacuum evaporator (Emitech K550). Samples were examined with the scanning electron microscope (Phillips XL30 TMP) at 10kV.

Results

Comparative Example 1 : Use of Span surfactants

When Span 85 was used as surfactant, Eudragit S100 appeared to produce aggregated particles when viewed under the optical microscope. SEM analysis confirmed the presence of semi-formed, aggregated particles, possibly originating from particle coalescence during solvent evaporation (see Fig. 1). It can be concluded that Span 85 does not stabilise the emulsion sufficiently to allow formation of discreet microparticles.

It would be desirable to produce particles using only ethanol as disperse phase solvent, to simplify the method of production and to reduce toxicity concerns due to any residual solvent in the microparticles, ethanol being less toxic than acetone and methanol. Therefore, 30mL portions of ethanol were used to dissolve 3 grams of L100-55, L100 and S100. The emulsification/solvent evaporation was used as before, with 200ml liquid paraffin containing 1% w/w Arlacel 83 as surfactant. SEMs of the microparticles are shown in Figs. 8A to 8C.

Conclusions

The SEMs show that for L100-55, L100 and S100 particles of excellent morphology can be used using a single, relatively non-toxic solvent.

Proof of concept: In-vitro drug release profiles

Attached are in-vitro drug release profiles for prednisolone loaded Eudragit L100 and S100 particles, in different pH media, using USPII paddle apparatus.

Examples 9-11

The microencapsulation of alternative pH-sensitive polymers, water insoluble polymers, and mixed water insoluble/pH-responsive polymers using sorbitan sesquioleate

As well as the microencapsulation of pH-sensitive Eudragits for site-specific drug delivery, it would be desirable to encapsulate a wide range of polymers, to achieve a universal method of microencapsulation. With this aim in mind, it was attempted to microencapsulate other polymers using the liquid paraffin/alcohol and acetone/Arlacel 83 emulsification/solvent evaporation method.

emulsification/solvent evaporation method may allow successful encapsulation with this polymer.

Example 11 : Use of Eudragit RS100 and mixtures of RS100 with L100 and S100

Microencapsulation of the water insoluble polymer Eudragit RS100 was tried alone, and in combination with L100 and S100. RS100 alone can be used for sustained release applications, and in combinations with the pH-sensitive eudragits may modify the release from these polymers. 3 grams RS100 was soluble in 30mL acetone and 30ml acetone/ethanol (1:1), but not 30mL ethanol. 1:1 mixtures of RS100/L100 and RS100/S100 were soluble in all three solvent mixtures. The SEMs of the products obtained are shown in Figs. 11A-11H.

Conclusions

The SEMs show that the method produces good particles when RS100 is used alone, or in combination with L100 or S100. It is expected that RS100 will retard the release of drug from a pH-responsive microparticulate system. The RS/S combination may allow for a sustained release of drug in the colonic region, as opposed to dose-dumping which may occur from a purely ph-responsive system. It is foreseeable that such a system would have benefits in the topical therapy of inflammatory bowel diseases, preventing a total premature release of drug and systemic absorption, but would be unlikely to be voided before significant drug release had occurred due to the prolonged colonic retention of small particulate systems.

Similarly, the mixture of RS/L may permit a controlled release throughout the length of the small intestine. Particles formed from RS100 may have sustained release applications, and also show the versatility of our method of microencapsulation, particularly for the Eudragit range of polymers.

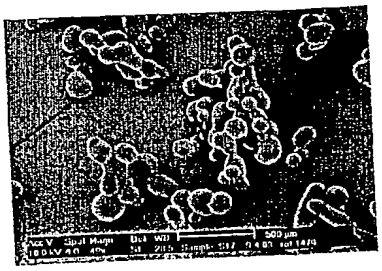

Fig 1: 1% span 85

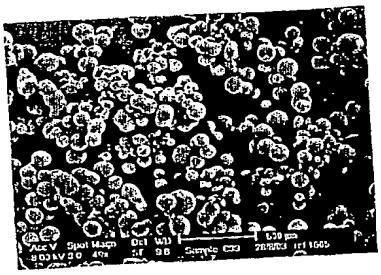

Fig 2A: 1% oleic acid

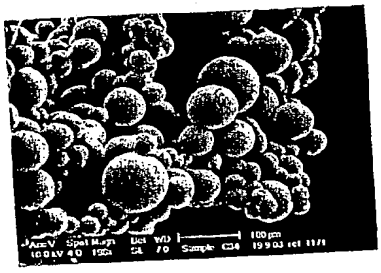

Fig 2B: 2% oleic acid

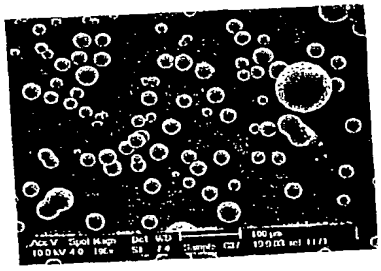

Fig 2C: 3% oleic acid

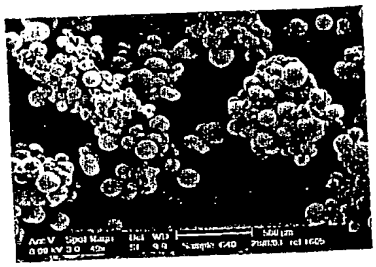

Fig 3A: 1% Brij 92

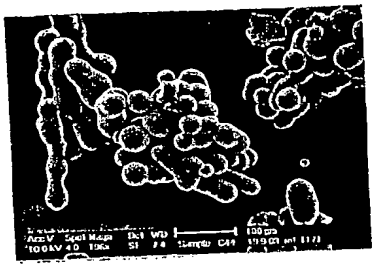

Fig 3B: 2% Brij 92

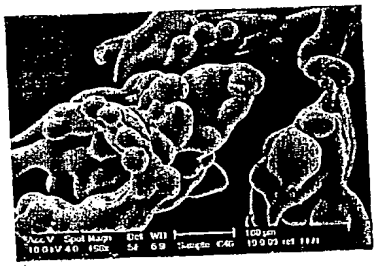

Fig 3C: 3% Brij 92

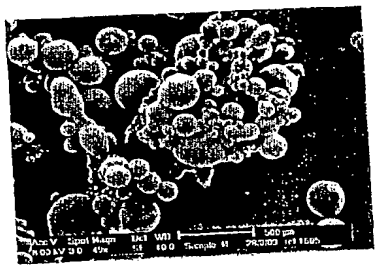

Fig 3D: 1% Brij 52 (dissolved in organic solvent phase)

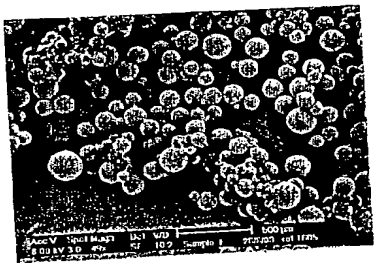

Fig 3E: 1% Brij 52 (heated)

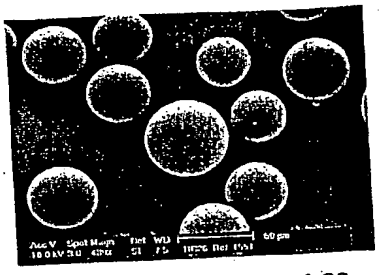

Fig 4A: 1% Arlacel 83

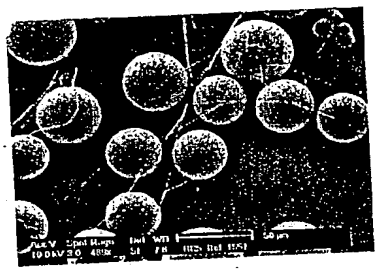

Fig 4B: 2% Arlacel 83

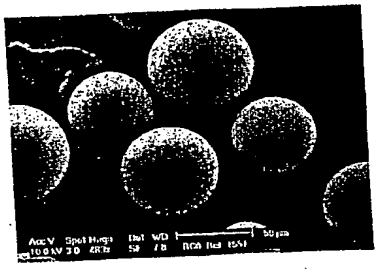

Fig 4C: 3% Arlacel 83

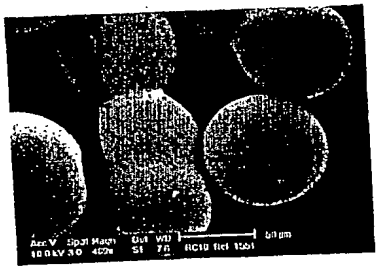

Fig 5: 1% (14.4% Tween 80 and 85.6% span 85)

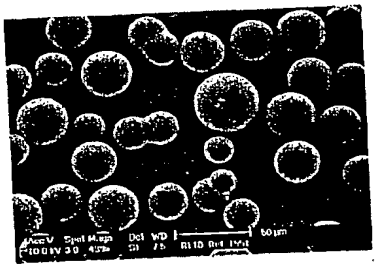

Fig 6: Eudragit L100/1% Arlacel 83/20mL acetone/10mL methanol

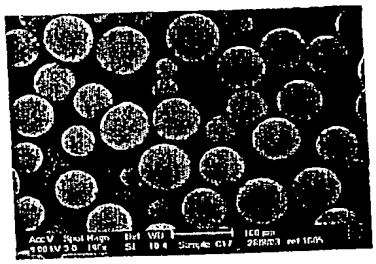

Fig 7A: 15mL acetone/15mL methanol

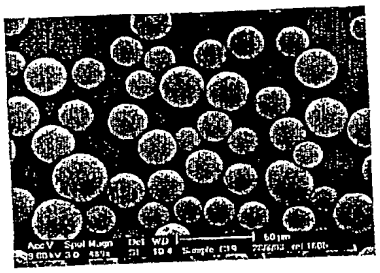

Fig 7B: 15mL acetone/15mL ethanol

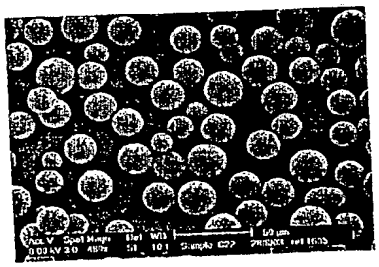

Fig 7C: 20mL acetone/10mL ethanol

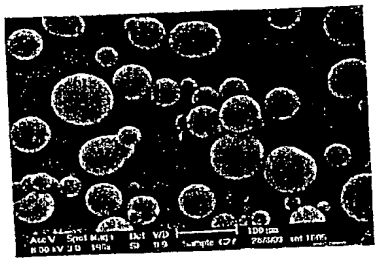

Fig 7D: 25mL acetone/5mL ethanol

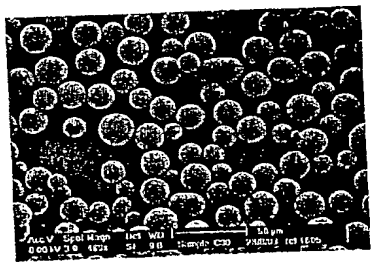

Fig 7E: 25mL acetone/5mL methanol

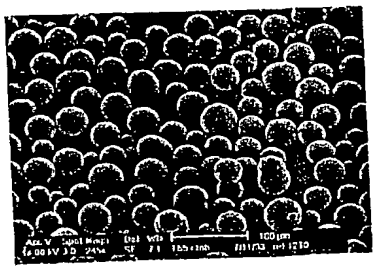

Fig 8A: 3g L100-55/30mL ethanol/1% Arlacel 83

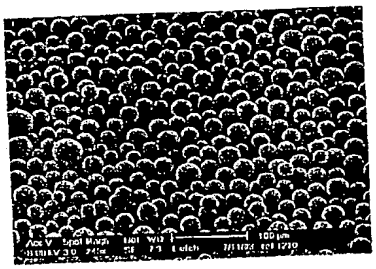

Fig 8B: 3g L100/30mL ethanol/1% Arlacel 83

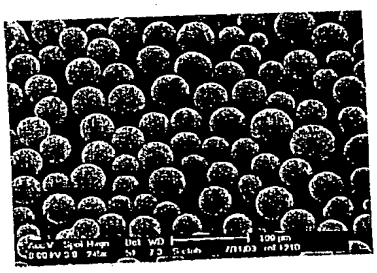

Fig 8C: 3g S100/30mL ethanol/1% Arlacel 83

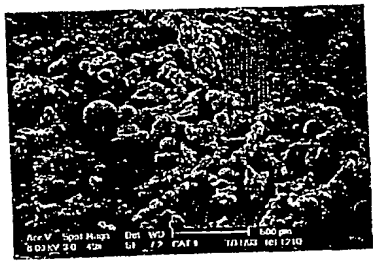

Fig 9: 3g CAT/30mL acetone/1% Arlacel 83

Fig 10: 3g HPMCP/30mL acetone/1% Arlacel 83

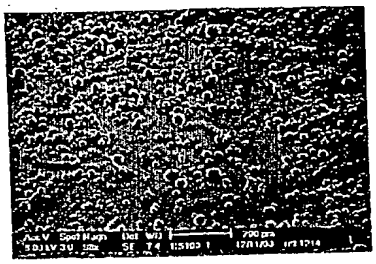

Fig 11A: 3g RS/30mL acetone

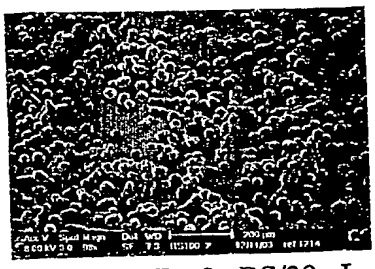

Fig 11B: 3g RS/30mL acetone/ethanol (1:1)

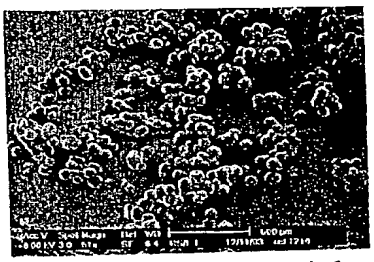

Fig 11C: RS/L acetone/ethanol (2:1)

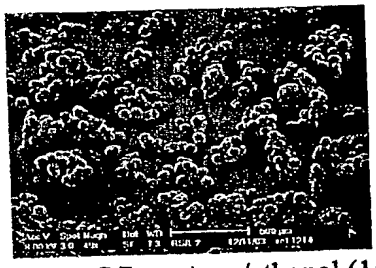

Fig 11D: RS/L acetone/ethanol (1:1)

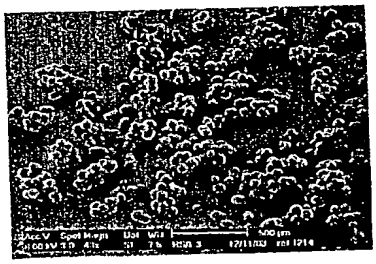

Fig 11E: RS/L acetone/ethanol (1:2)

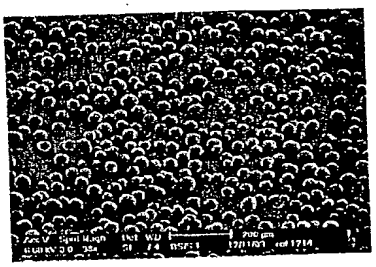

Fig 11F: RS/S acetone/ethanol (2:1)

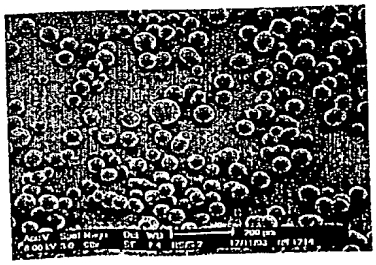

Fig 11G: RS/S acetone/ethanol (1:1)

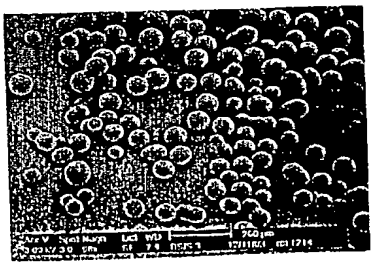

Fig 11H: RS/S acetone/ethanol (1:2)